Group Analysis

File: GroupAna.pdf

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SSCC/NIMH/NIH/HHS

FMRI Study Streamline

Experiment Design

↓

Scanning

↓

Pre-Processing

↓

Individual Subject Analysis

↓

Group Analysis

↓

Post-Processing: clusterization,
ROI analysis, connectivity, …

Preview

- Introduction: basic concepts
  - Why do we need to do group analysis?
  - Factor, quantitative covariates, main effect, interaction, …
- Various group analysis approaches
  - Regression (*t*-test): 3dttest++, 3dMEMA, 3dttest, 3RegAna
  - AN(C)OVA: 3dANOVAx, 3dMVM, GroupAna
  - Quantitative covariates: 3dttest++, 3dMEMA, 3dMVM, 3dLME
  - Complicated cases: 3dLME
- Miscellaneous
  - Issues regarding result reporting
  - Intra-Class Correlation (ICC)
  - Nonparametric approach and fixed-effects analysis

Why Group Analysis?

- Evolution of FMRI studies
  - Early days: no need for group analysis
    - Seed-based correlation for one subject was revolutionary
  - Now: torture brain/data enough, and hope nature will confess!
    - Many ways to manipulate the brain (and data)
- Reproducibility and generalization
  - Science strives for generality: summarizing subject results
  - Typically 10 or more subjects per group
  - Exceptions: pre-surgical planning, lie detection, …
- Why not one analysis with a mega model for all subjects?
  - Computationally unmanageable
  - Heterogeneity in data or experiment design across subjects

Toy example of group analysis

- Responses from a group of subjects under one condition
  - What we have: (β_1, β_2, …, β_{10})=(1.13, 0.87, …, 0.72)
- Centroid: average (β_1+β_2+…+β_{10})/10 = 0.92 is not enough
  - Variation/reliability measure: diversity, spread, deviation
- Model building
  - Subject *i*'s response = group average + deviation of subject *i*: simple model GLM (one-sample *t*-test)

$$\hat{\beta}_i = b + \epsilon_i, \epsilon_i \sim N(0, \sigma^2)$$

  - If individual responses are consistent, ϵ_i should be small
  - How small do we consider comfortable (*p*-value)?
    - *t*-test: significance measure = $\frac{\hat{b}}{\hat{\sigma}/n}$
- 2 measures: *b* (dimensional) and *t* (dimensionless)

Group Analysis Modes

- Conventional: voxel-wise (brain) or node-wise (surface)
  - Common effects are of interest
  - Cross-subjects variability should be properly accounted for
    - Appropriate model (program)
    - But variability is not typically discussed
  - With-subject correlation should also be accounted for
    - Between- vs. within-subject (repeated-measures) factors
    - Traditionally this is handled through ANOVA: syntactic sugar
    - GLM and LME
- Results: two components (on afni: OLay + Thr)
  - Effect estimates: have unit and physical meaning
  - Their significance (response to house **significantly** > face)
    - Very unfortunately p-values solely focused in FMRI!!!

Group Analysis Modes

- Conventional: voxel-wise (brain) or node-wise (surface)
  - Prerequisite: reasonable alignment to some template
  - Limitations: alignment could be suboptimal or even poor
    - Different folding patterns across subjects: better alignment could help
    - Different cytoarchitectonic (or functional) locations across subjects: alignment won't help!
    - Impact on conjunction vs. selectivity
- Alternatives (won't discuss)
  - ROI-based approach
    - Half data for functional localizers, and half for ROI analysis
    - Easier: whole brain reduced to one or a few numbers per subject
    - Model building and tuning possible

Terminology: Explanatory variables

- Response/Outcome variable: regression coeficients
- Factor: categorical, qualitative, nominal or discrete variable
  - Categorization of conditions/tasks
    - Within-subject (repeated-measures) factor
  - Subject-grouping: Group of subjects (gender, normal/patients)
    - Between-subject factor
    - Gender, patients/controls, genotypes, …
  - Subject: random factor measuring deviations
    - Of no interest, but served as random samples from a population
- Quantitative (numeric or continuous) covariate
  - Three usages of 'covariate'
    - Quantitative
    - Variable of no interest: qualitative (scanner, sex, handedness) or quantitative
    - Explanatory variable (regressor, independent variable, or predictor)
  - Examples: age, IQ, reaction time, *etc*.

Terminology: Fixed effects

- Fixed factor: categorical (qualitative or discrete) variable
  - Treated as a fixed variable (constant to be estimated) in the model
    - Categorization of conditions/tasks (modality: visual/auditory)
      - Within-subject (repeated-measures) factor: 3 emotions
    - Subject-grouping: Group of subjects (gender, normal/patients)
      - Between-subject factor
  - All levels of a factor are of interest
    - main effect, contrasts among levels
  - Fixed in the sense of statistical inferences
    - apply only to the specific levels of the factor
      - Emotions: positive, negative, neutral
    - Don’t extend to other potential levels that might have been included
      - Inferences on positive and negative emotions can’t be generated to neutral
- Fixed variable: quantitative covariate

Terminology: Random effects

- Random factor/effect
  - Random variable in the model: exclusively subject in FMRI
    - average + effects uniquely attributable to each subject: *e.g.* $N(\mu, \tau^2)$
    - Requires enough number of subjects
  - Each individual subject effect is of NO interest
    - Group response = 0.92%, subject 1 = 1,13%, random effect = 0.21%
  - Random in the sense
    - Subjects as random samples (representations) from a population
    - Inferences can be generalized to a hypothetical population
- A generic model: decomposing each subject's response $\boldsymbol{y}_i = X_i\boldsymbol{\beta} + Z_i\boldsymbol{b}_i + \boldsymbol{\epsilon}_i$
  - Fixed (population) effects: universal constants (immutable): $\boldsymbol{\beta}$
  - Random effects: individual subject's deviation from the population (personality: durable): $\boldsymbol{b}_i$
  - Residuals: noise (evanescent): $\boldsymbol{\epsilon}_i$

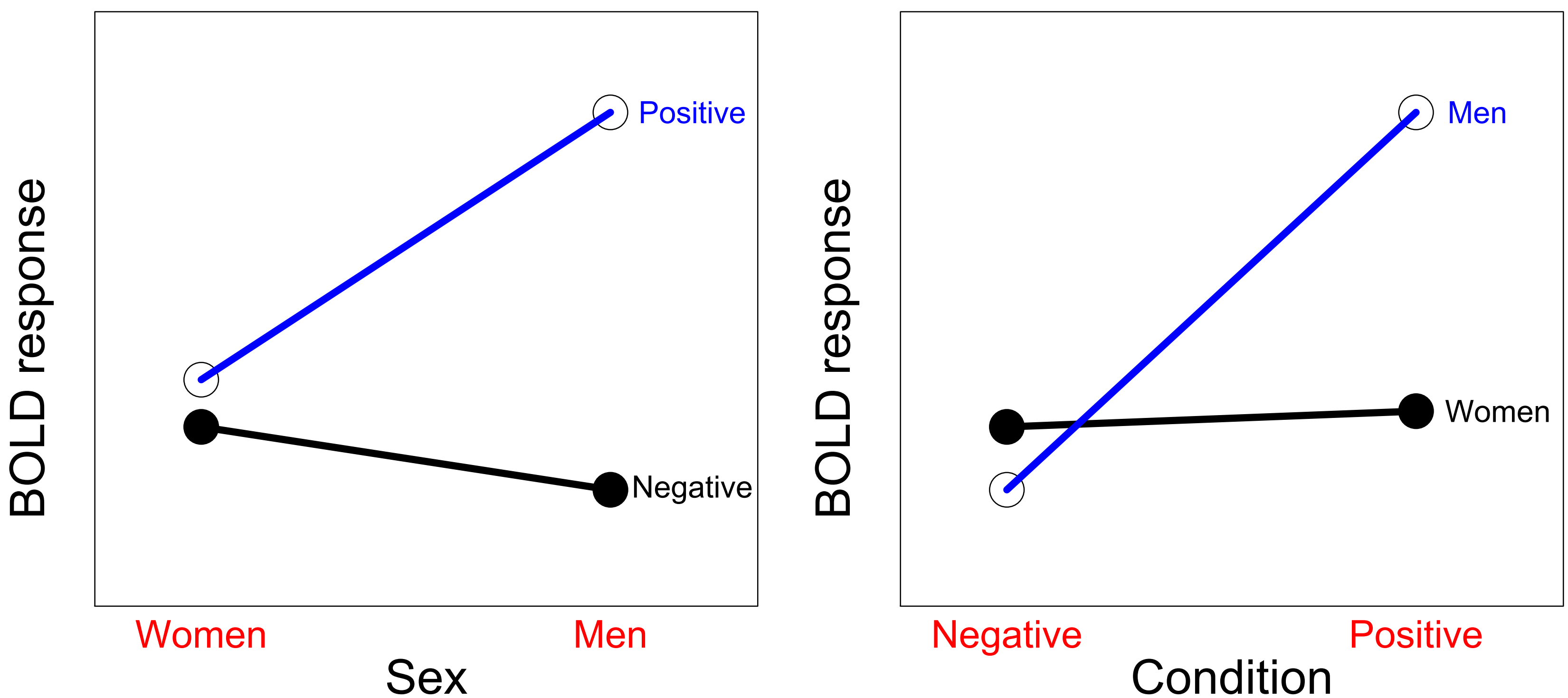
Terminology: Omnibus tests - main effect and interaction

- Main effect: any difference across levels of a factor?
- Interactions: with ≥ 2 factors, interaction may exist
  - 2 × 2 design: F-test for interaction between A and B = t-test of

    (A1B1 - A1B2) - (A2B1 - A2B2) or (A1B1 - A2B1) - (A1B2 - A2B2)

    - t is better than F: a positive t shows

      A1B1 - A1B2 > A2B1 - A2B2 and A1B1 - A2B1 > A1B2 - A2B2

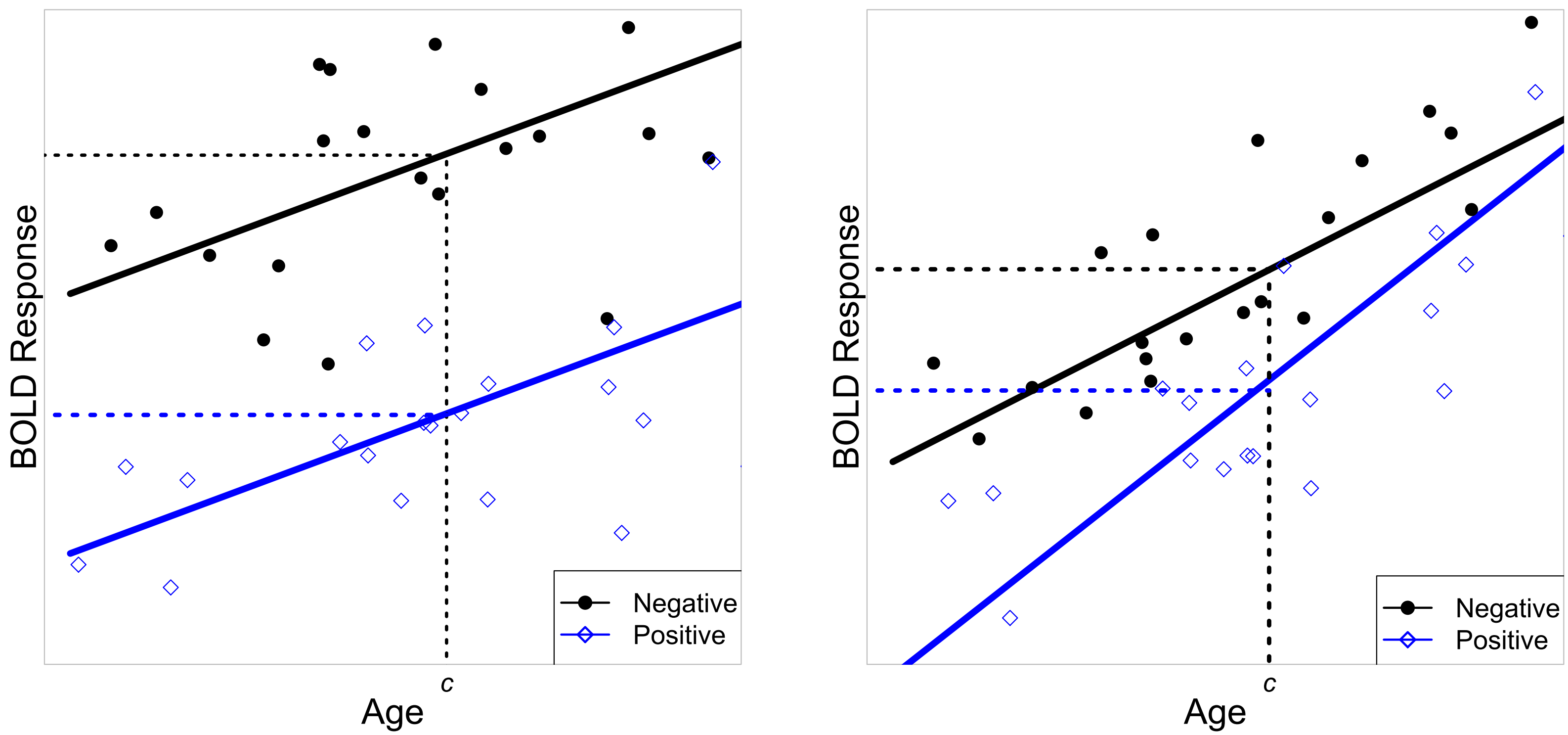


Terminology: Interaction

- Interactions: ≥ 2 factors
  - May become very difficult to sort out!
    - ≥ 3 levels in a factor
    - ≥ 3 factors
  - Solutions: reduction
    - Pairwise comparison
    - Plotting: ROI (Figures don't lie, but liars do figure. Mark Twain)
  - Requires sophisticated modeling
    - AN(C)OVA: 3dANOVAx, 3dMVM, 3dLME
- Interactions: quantitative covariates
  - In addition to linear effects, may have nonlinearity: $x_1 * x_2$, or x^2

Terminology: Interaction

- Interaction: between a factor and a quantitative covariate



- Throw in an explanatory variable in a model as a nuisance regressor (additive effect) may not be enough
  - Model building/tuning: Potential interactions with other explanatory variables?
  - Of scientific interest (e.g., gender difference)

Models at Group Level

- Conventional approach: taking β (or linear combination of multiple β's) only for group analysis
  - Assumption: all subjects have same precision (reliability, standard error, confidence interval) about β
  - All subjects are treated equally
  - Student *t*-test: paired, one- and two-sample: not random-effects models in strict sense as usually claimed
  - AN(C)OVA, GLM, MVM, LME
- Alternative: taking both effect estimates and *t*-statistics
  - *t*-statistic contains precision information about effect estimates
  - Each subject is weighted based on precision of effect estimate
- All models are some sorts of linear model
  - *t*-test, ANOVA, MVM, LME, MEMA
  - Partition each subject's effect into multiple components

One-Sample Case

- One group of subjects ($n \geq 10$)
  - One condition (visual or auditory) effect
  - Linear combination of multiple effects (visual vs. auditory)
- Null hypothesis H_0: average effect = 0
  - Rejecting H_0 is of interest!
- Results
  - Average effect at group level (OLay)
  - Significance: t-statistic (Thr - Two-tailed by default)
- Approaches
  - uber_ttest.py, 3dttest++ (3dttest), 3dMEMA

One-Sample Case: Example

- 3dttest++: taking β only for group analysis

```
3dttest++ -prefix VisGroup -mask mask+tlrc \
 -setA 'FP+tlrc[Vrel#0_Coef]'          \
       'FR+tlrc[Vrel#0_Coef]'          \
       ......
       'GM+tlrc[Vrel#0_Coef]'
```

- 3dMEMA: taking β and *t*-statistic for group analysis

```
3dMEMA -prefix VisGroupMEMA -mask mask+tlrc -setA Vis \
 FP 'FP+tlrc[Vrel#0_Coef]' 'FP+tlrc[Vrel#0_Tstat]'    \
 FR 'FR+tlrc[Vrel#0_Coef]' 'FR+tlrc[Vrel#0_Tstat]'    \
       ......
 GM 'GM+tlrc[Vrel#0_Coef]' 'GM+tlrc[Vrel#0_Tstat]'    \
 -missing_data 0
```

Two-Sample Case

- Two groups of subjects ($n \geq 10$): males and females
  - One condition (visual or auditory) effect
  - Linear combination of multiple effects (visual vs. auditory)
  - Example: Gender difference in emotion effect?
- Null hypothesis H_0: Group1 = Group2
  - Results
    - Group difference in average effect
    - Significance: *t*-statistic - Two-tailed by default
- Approaches
  - uber_ttest.py, 3dttest++, 3dMEMA
  - One-way between-subjects ANOVA
    - 3dANOVA: can also obtain individual group test
    - 3dANOVA3: group by condition interaction

Paired Case

- One groups of subjects ($n \geq 10$)
  - 2 conditions (visual or auditory): no missing data allowed (3dLME)
  - Example: Visual vs. Auditory
- Null hypothesis H_0: Condition1 = Condition2
  - Results
    - Average difference at group level
    - Significance: *t*-statistic (two-tailed by default)
- Approaches
  - uber_ttest.py, 3dttest++ (3dttest), 3dMEMA
  - One-way within-subject (repeated-measures) ANOVA
    - 3dANOVA2 –type 3: can also obtain individual condition test
  - Missing data (3dLME): only 10 among 20 subjects have both
- Essentially equivalent to one-sample case: use contrast as input

Paired Case: Example

- 3dttest++: comparing two conditions

```
3dttest++ -prefix Vis_Aud            \
  -mask mask+tlrc -paired            \
  -setA 'FP+tlrc[Vrel#0_Coef]'       \
        'FR+tlrc[Vrel#0_Coef]'       \
        ......
        'GM+tlrc[Vrel#0_Coef]'       \
  -setB 'FP+tlrc[Arel#0_Coef]'       \
        'FR+tlrc[Arel#0_Coef]'       \
        ......
        'GM+tlrc[Arel#0_Coef]'
```

Paired Case: Example

- 3dMEMA: comparing two conditions
  - Contrast has to come from each subject

```
3dMEMA -prefix Vis_Aud_MEMA                    \
 -mask mask+tlrc -missing_data 0               \
 -setA Vis-Aud                                 \
 FP 'FP+tlrc[Vrel-Arel#0_Coef]' 'FP+tlrc[Vrel-Arel#0_Tstat]' \
 FR 'FR+tlrc[Vrel-Arel#0_Coef]' 'FR+tlrc[Vrel-Arel#0_Tstat]' \
 ……
 GM 'GM+tlrc[Vrel-Arel#0_Coef]' 'GM+tlrc[Vrel-Arel#0_Tstat]'
```

One-Way Between-Subjects ANOVA

- Two or more groups of subjects ($n \geq 10$)
  - One condition or linear combination of multiple conditions
  - Example: visual, auditory, or visual vs. auditory
- Null hypothesis H_0: Group1 = Group2
  - Results
    - Average group difference
    - Significance: t- and F-statistic (two-tailed by default)
- Approaches
  - 3dANOVA
  - > 2 groups: pair-group contrasts - 3dttest++ (3dttest), 3dMEMA
  - Dummy coding: 3dttest++, 3dMEMA
  - 3dMVM (not recommended)

Multiple-Way Between-Subjects ANOVA

- Two or more subject-grouping factors: factorial
  - One condition or linear combination of multiple conditions
  - Example: gender, control/patient, genotype, handedness, …
- Testing main effects, interactions, single group, group comparisons
  - Significance: *t*- (two-tailed by default) and *F*-statistic
- Approaches
  - Factorial design (imbalance not allowed): two-way (3dANOVA2 – type 1), three-way (3dANOVA3 –type 1)
  - 3dMVM: no limit on number of factors (imbalance allowed)
  - All factors have two levels: uber_ttest.py, 3dttest++, 3dMEMA
  - Using group coding with 3dttest++, 3dMEMA: imbalance allowed

One-Way Within-Subject ANOVA

- Also called one-way repeated-measures: one group of subject ($n \geq 10$)
  - Two or more conditions: extension to paired *t*-test
  - Example: happy, sad, neutral
- Main effect, simple effects, contrasts, general linear tests,
  - Significance: *t*- (two-tailed by default) and F-statistic
- Approaches
  - 3dANOVA2 -type 3 (two-way ANOVA with one random factor)
  - With two conditions, equivalent to paired case with 3dttest++ (3dttest), 3dMEMA
  - With more than two conditions, can break into pairwise comparisons with 3dttest++, 3dMEMA

One-Way Within-Subject ANOVA

- Example: visual vs. auditory condition

```
3dANOVA2 -type 3 -alevels 2 -blevels 10      \
 -prefix Vis_Aud -mask mask+tlrc             \
  -dset 1 1  'FP+tlrc[Vrel#0_Coef]'    \
  -dset 1 2  'FR+tlrc[Vrel#0_Coef]'    \
      ......
  -dset 1 10 'GM+tlrc[Vrel#0_Coef]'    \
  -dset 2 1  'FP+tlrc[Arel#0_Coef]'    \
  -dset 2 2  'FR+tlrc[Arel#0_Coef]'    \
      ......
  -dset 2 10 'GM+tlrc[Arel#0_Coef]'    \
```

Two-Way Within-Subject ANOVA

- Factorial design; also known as two-way repeated-measures
  - 2 within-subject factors
  - Example: emotion and category (visual/auditory)
- Testing main effects, interactions, simple effects, contrasts
  - Significance: *t*- (two-tailed by default) and F-statistic
- Approaches
  - 3dANOVA3 –type 4 (three-way ANOVA with one random factor)
  - All factors have 2 levels (2x2): uber_ttest.py, 3dttest++, 3dMEMA
  - Missing data?
    - Break into t-tests: uber_ttest.py, 3dttest++ (3dttest), 3dMEMA

Two-Way Mixed ANOVA

- Factorial design
  - One between-subjects and one within-subject factor
  - Example: gender (male and female) and emotion (happy, sad, neutral)
- Testing main effects, interactions, simple effects, contrasts
  - Significance: *t*- (two-tailed by default) and *F*-statistic
- Approaches
  - 3dANOVA3 –type 5 (three-way ANOVA with one random factor)
  - If all factors have 2 levels (2x2): 3dttest++, 3dMEMA
  - Missing data?
    - Unequal number of subjects across groups: 3dMVM, GroupAna
    - Break into *t*-tests: uber_ttest.py, 3dttest++ (3dttest), 3dMEMA
    - 3dLME

Group analysis with multiple basis functions

- Basis functions: TENTzero, TENT, CSPLINzero, CSPLIN
  - Area under the curve (AUC) approach
    - Forget about the subtle shape difference
    - Focus on the response magnitude measured by AUC
    - Potential issues: Shape information lost; Undershoot may cause trouble
  - Maintaining shape information
    - Taking individual β values to group analysis
- Basis functions of SPMG2/3
  - Only take the major component to group level
  - Reconstruct the HRF, and take the effect estimates at the time grids to group analysis

Group analysis with multiple basis functions

- Analysis with effect estimates at consecutive time grids
  - Used to be considered very difficult
  - Extra variable, Time = t_0, t_1, …, t_k
  - One group of subjects under one condition
    - Null hypothesis H_0: $\beta_1=0, \beta_2=0, \ldots, \beta_k=0$ (NOT $\beta_1=\beta_2=\ldots=\beta_k$)
    - Use 3dLME or 3dMVM
    - Result: F-statistic for H_0 and t-statistic for each time grid
  - Multiple groups under one condition
    - Use 3dANOVA3 –type 5 (two-way mixed ANOVA) or 3dMVM
    - Focus: do these groups have different response shape?
      - Null hypothesis H_0: $\beta_1^{(1)}=\beta_1^{(2)}, \beta_2^{(1)}=\beta_2^{(2)}, \ldots, \beta_k^{(1)}=\beta_k^{(2)}$
      - F-statistic for the interaction between Time and Group
      - F-statistic for Group: AUC; F-statistic for Time: ?
    - Subtle shape differences: t-statistic for each time grid of each group

Group analysis with multiple basis functions

- Analysis with effect estimates at consecutive time grids
  - One groups under multiple conditions
    - Use 3dANOVA3 –type 4 or 3dMVM
    - Focus: do these conditions have different response shape?
      - Null hypothesis H_0: $\beta_1^{(1)} = \beta_1^{(2)}, \beta_2^{(1)} = \beta_2^{(2)}, ..., \beta_k^{(1)} = \beta_k^{(2)}$
      - F-statistic for the interaction between Time and Condition
      - F-statistic for Condition: AUC; F-statistic for Time: ?
    - Subtle shape differences: t for each time grid of the condition
  - Complicated scenarios: 3dMVM
    - Unequal number of subjects across groups
    - Comparing shape across groups and conditions simultaneously
    - More factors or between-subjects quantitative variables: age, IQ

More sophisticated cases?

- 3dMVM
    - No bound on the number of explanatory variables
    - Three tests: UVT-UC, UVT-SC, MVT
    - Between-subjects covariates allowed
- If all factors have two levels, run 3dttest++, 3dMEMA
- Try to break into multiple *t*-tests: uber_ttest.py, 3dttest++, 3dMEMA
- 3dLME
    - Within-subject covariates allowed
    - Missing data of a within-subject factor
    - Subjects are family members or even twins

Correlation analysis

- Correlation between brain response and behavioral measures

$$\hat{\beta}_i = \alpha_0 + \alpha_1 * x_i + \epsilon_i$$

  - Difference between correlation and regression?
    - Essentially the same
    - When explanatory and response variable are standardized, the regression coefficient = correlation coefficient
  - Two approaches
    - Standardization
    - Convert *t*-statistic to *r* (or determination coefficient)

$$R^2 = t^2/(t^2 + DF)$$

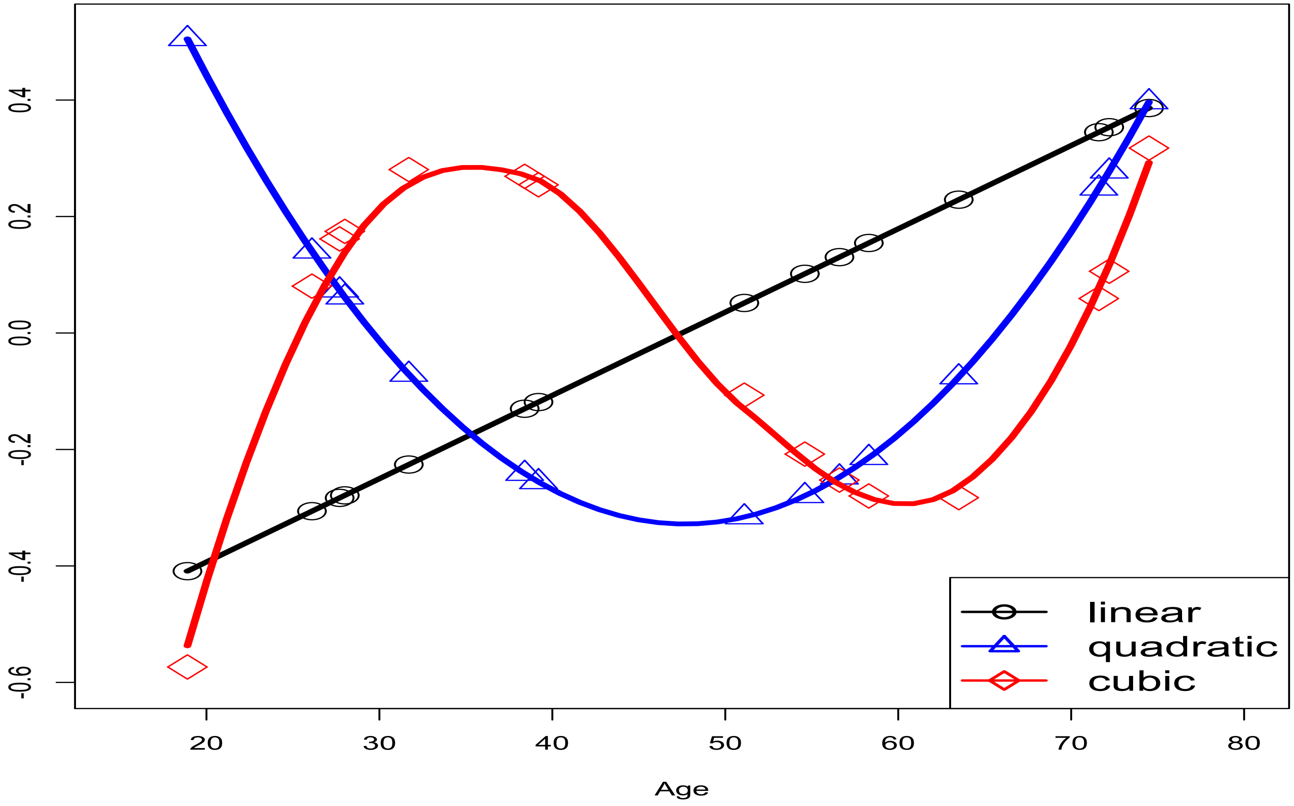
    - Programs: 3dttest++, 3dMEMA, 3dMVM, 3dRegAna

Trend analysis

- Correlation between brain response and some gradation
  - Linear, quadratic, or higher-order effects
    - Between-subjects: Age, IQ
      - Fixed effect
    - Within-subject measures: morphed images
      - Random effects involved: 3dLME
  - Modeling: weights based on gradation
    - Equally-spaced: coefficients from orthogonal polynomials
    - With 6 equally-spaced levels, *e.g.*, 0, 20, 40, 60, 80, 100%,
      - Linear: -5 -3 -1 1 3 5
      - Quadratic: 5 -1 -4 -4 -1 5
      - Cubic: -5 7 4 -4 -7 5

Trend analysis

- Correlation between brain response and some gradation
  - Modeling: weights based on gradation
    - Not equally-spaced: constructed from, *e.g.*, poly() in R
    - Ages of 15 subjects: 31.7 38.4 51.1 72.2 27.7 71.6 74.5 56.6 54.6 18.9 28.0 26.1 58.3 39.2 63.5



Trend analysis

- Correlation between brain response and some gradation
  - Modeling with within-subject trend
    - Run GLT with appropriate weights
  - Modeling with within-subject trend: 3 approaches
    - Set up GLT among the factor levels at group level using the weights
      - 3dANOVA2/3, 3dMVM
    - Set up the weights as the values of a variable
      - Needs to account for deviation of each subject
      - 3dLME
    - Run trend analysis at individual level (*i.e.*, -gltsym), and then take the trend effect estimates to group level
      - Simpler than the other two approaches

Group analysis with quantitative variables

- Covariate: 3 usages
  - Quantitative (vs. categorical) variable
    - Age, IQ, behavioral measures, …
  - Of no interest to the investigator
    - Age, IQ, sex, handedness, scanner,…
  - Any explanatory variables in a model
- Variable selection
  - Infinite candidates: relying on prior information
  - Typical choices: age, IQ, RT, …
  - RT: individual vs. group level
    - Amplitude modulation: cross-trial variability at individual level
    - Group level: variability across subjects

Group analysis with quantitative variables

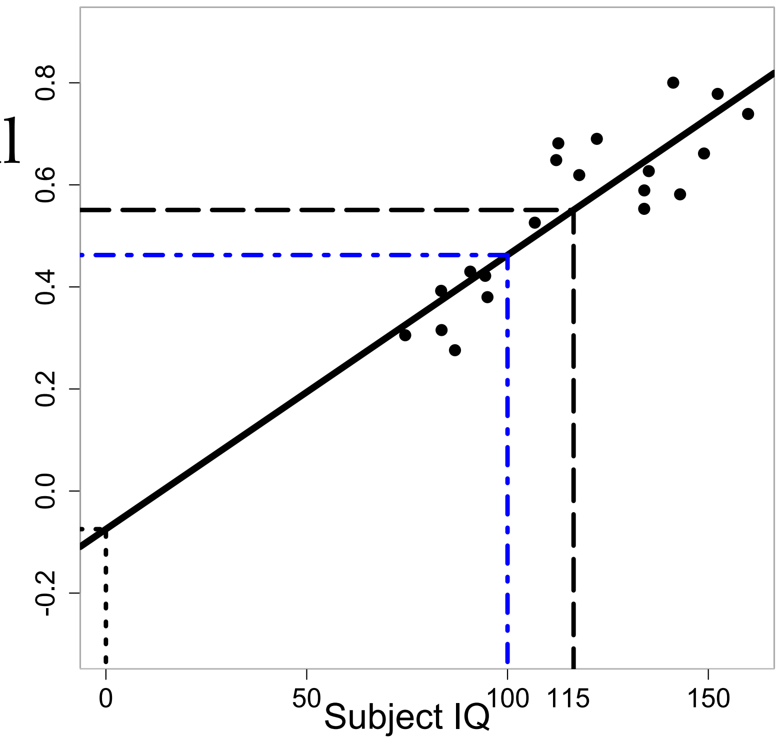
- Conventional framework
  - ANCOVA: one between-subjects factor (e.g., sex) + one quantitative variable (e.g., age)
    - Extension to ANOVA: GLM
    - Homogeneity of slopes
- Broader framework
  - Any modeling approaches involving quantitative variables
    - Regression, GLM, MVM, LME
    - Trend analysis, correlation analysis

Quantitative variables: subtleties

- Regression: one group of subjects + quantitative variables

$$\hat{\beta}_i = \alpha_0 + \alpha_1 * x_{1i} + \alpha_2 * x_{2i} + \epsilon_i$$

- Interpretation of effects
  - α_1 - slope (change rate, marginal effect): effect per unit of x
  - α_0 – intercept: group effect while x=0
    - Not necessarily meaningful
    - Linearity may not hold
    - Solution: centering - crucial for interpretability
    - Mean centering?

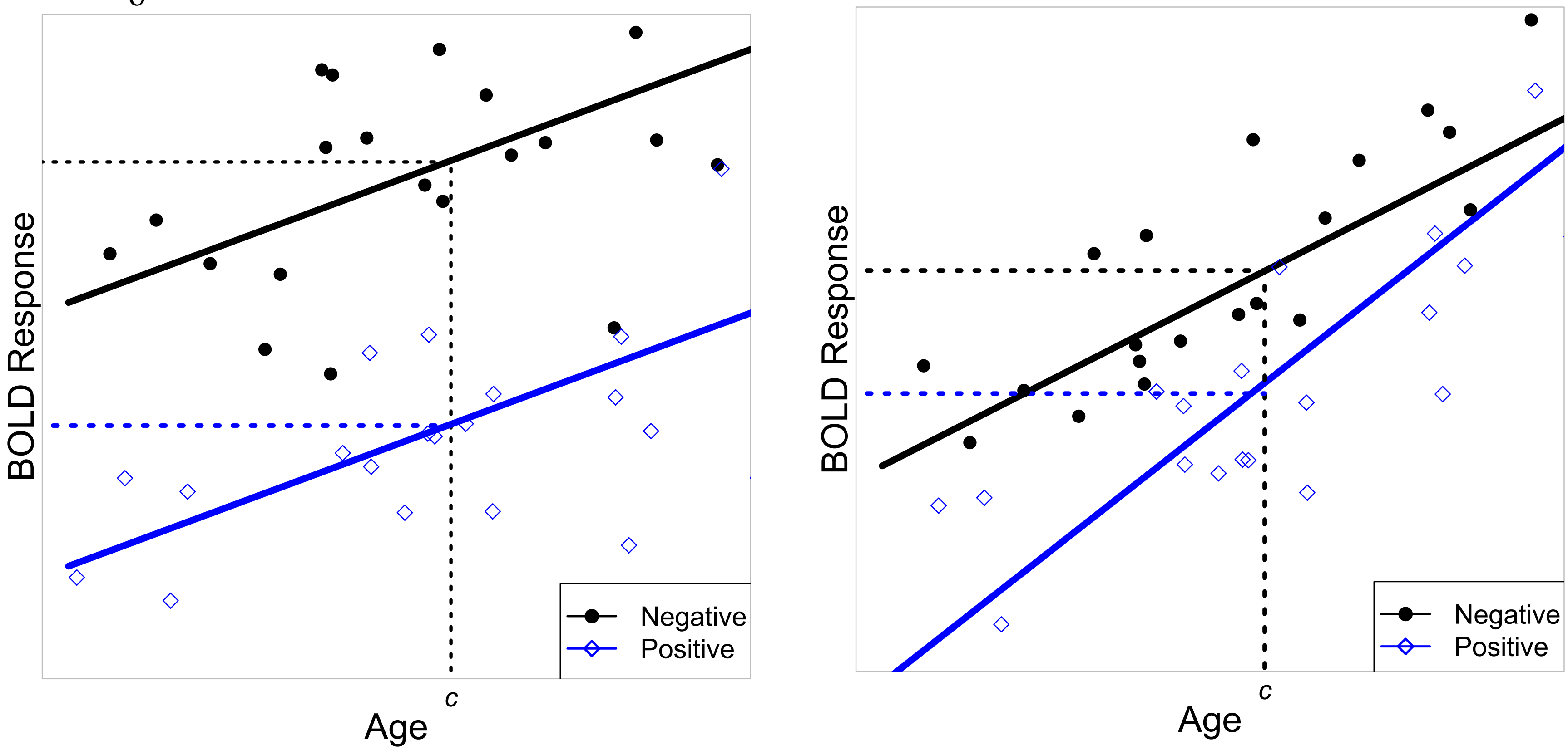


Quantitative variables: subtleties

- Trickier scenarios with two or more groups

$$\hat{\beta}_i = \alpha_0 + \alpha_1 * x_{1i} + \alpha_2 * x_{2i} + \alpha_3 * x_{3i} + \epsilon_{ij}$$

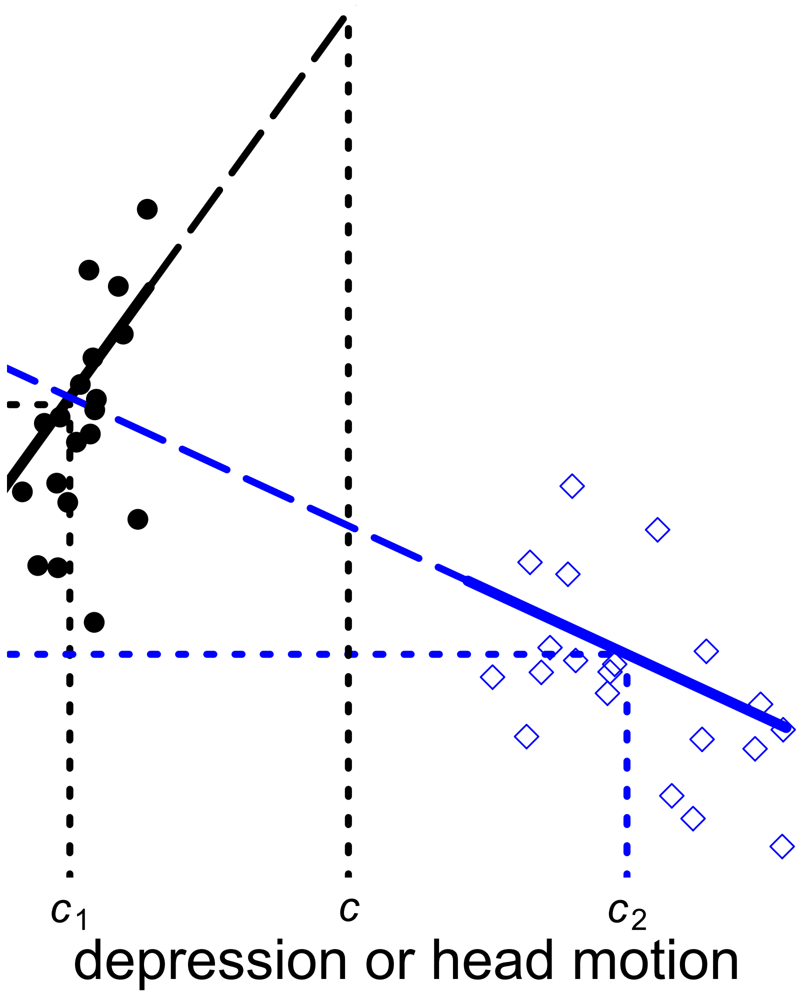
  - Interpretation of effects
    - Slope: Interaction! Same or different slope?
    - α_0 – same or different center?



Quantitative variables: subtleties

- Trickiest scenario with two or more groups

$$\hat{\beta}_i = \alpha_0 + \alpha_1 * x_{1i} + \alpha_2 * x_{2i} + \alpha_3 * x_{3i} + \epsilon_{ij}$$

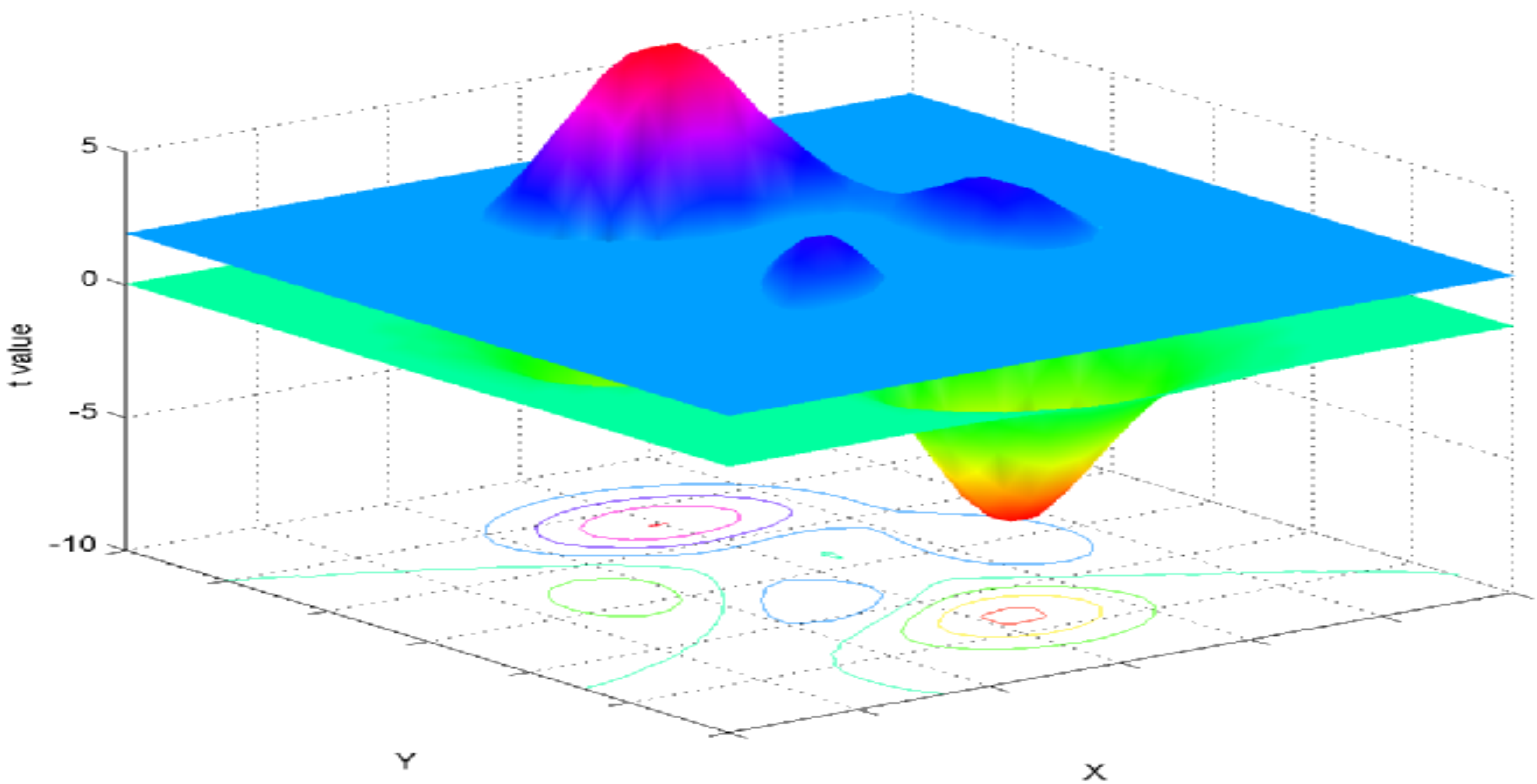


Why should we report response magnitudes?

- Unacceptable in some fields if only significance is reported
- Too much obsession or worship in FMRI about *p*-value!
  - Colored blobs of *t*-values
  - Peak voxel selected based on peak *t*-value
- Science is about reproducibility
  - Response amplitude should be of primacy focus
  - Statistics are only for thresholding
    - No physical dimension
    - Once surviving threshold, specific values are not informative
  - Should science be based on a dichotomous inference?
    - If a cluster fails to survive for thresholding, there is no value?
    - SVC: Band-Aid solution
    - More honest approach: response amplitudes

• **Basics: Null hypothesis significance testing (NHST)**

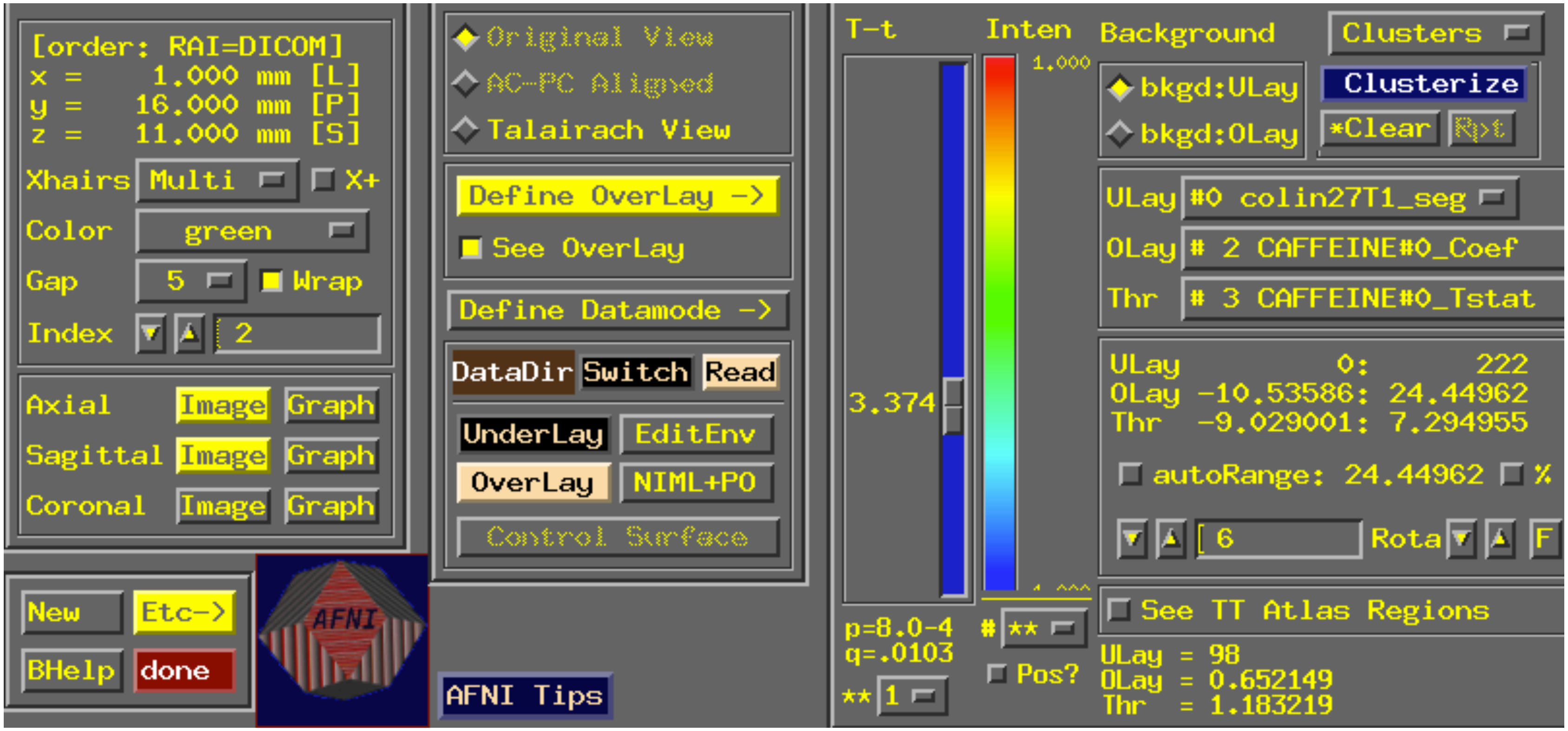
- Null and alternative hypotheses
  - $\mathbf{H_0}$: nothing happened vs. $\mathbf{H_1}$: something happened
- Dichotomous or binary decision



How rigorous about corrections?

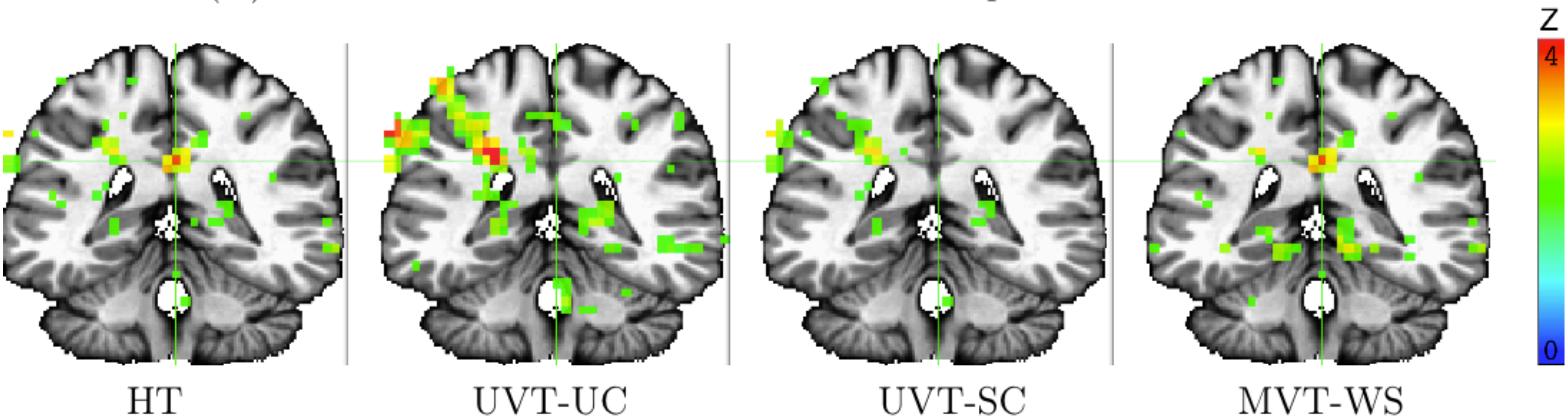
- Two types of correction
  - Multiple testing correction n(MTC): same test across brain
    - FWE, FDR, SVC(?)
    - People (esp. reviewers) worship this!
  - Multiple comparisons correction (MCC): different tests
    - Happy vs. Sad, Happy vs. Neutral, Sad vs. Neutral
    - Two one-sided *t*-tests: p-value is ½ of two-sided test!
    - How far do you want to go?
      - Tests in one study
      - Tests in all FMRI or all scientific studies?
    - Nobody cares the issue in FMRI
- Many reasons for correction failure
  - Region size, number of subjects, alignment quality, substantial cross-subject variability (anxiety disorder, depression, …)

Presenting response magnitudes



Presenting response magnitudes

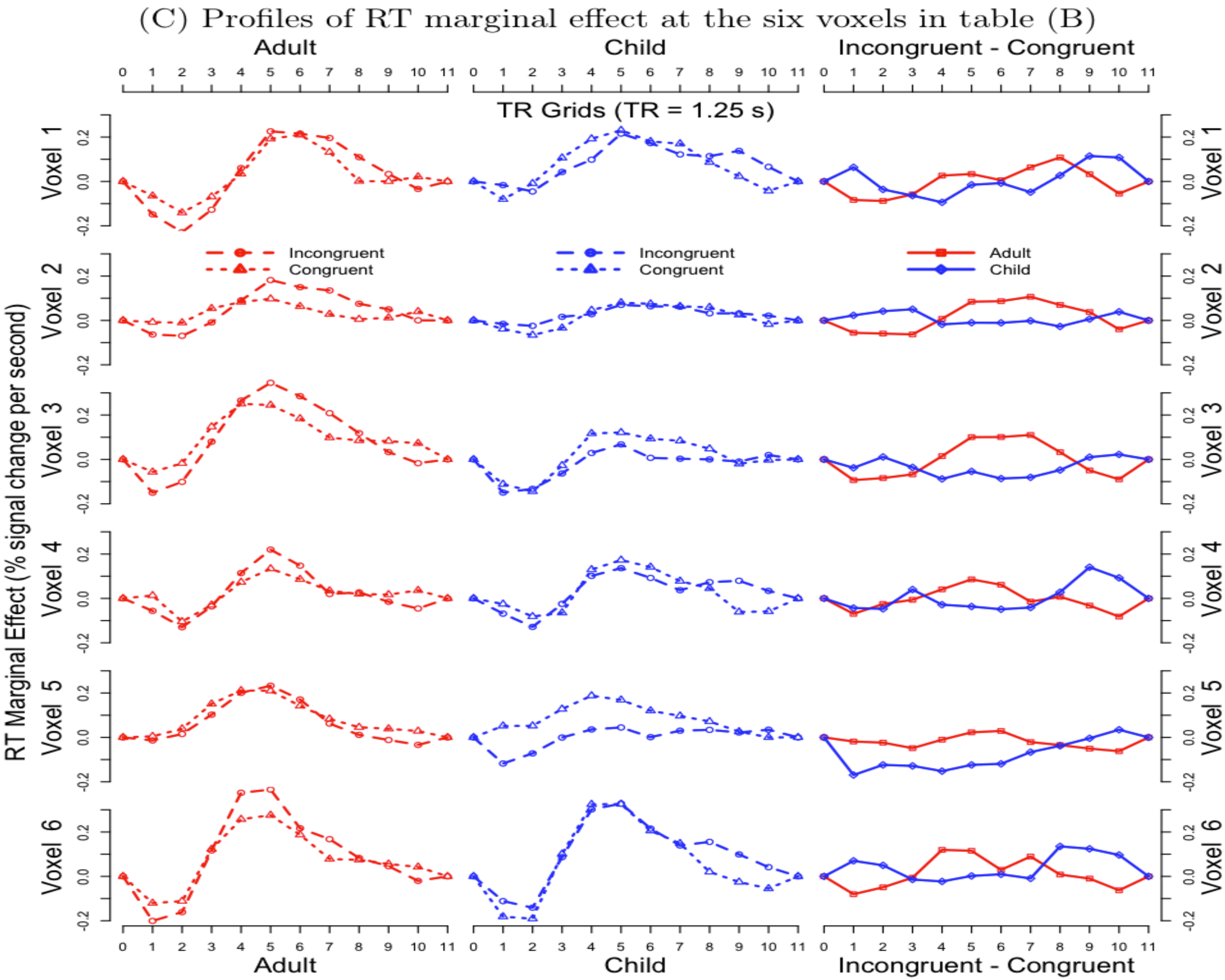
(A) Coronal view of interaction effect of Group:Condition:Time



(B) Sphericity scenarios at six representative voxels

Voxel		Sphericity			**UVT-UC**	**UVT-SC**	**MVT-WS**	**HT**
No.	coordinates	Mauchly p-value	ϵ_{GG}	ϵ_{HF}	p-value	p-value	p-value	taking
1	-2 36 27	0	0.32	0.35	0.28	0.31	0.00021	MVT-WS
2	-33 -5 42	0	0.42	0.46	3.8×10^{-6}	8.4×10^{-4}	1.6×10^{-4}	MVT-WS
3	-50 -16 24	0	0.45	0.50	1.6×10^{-4}	0.0041	0.14	MVT-WS
4	-5 -20 23	8.7×10^{-6}	0.68	0.79	1.8×10^{-5}	0.0001	0.008	UVT-SC
5	37 68 20	0	0.30	0.32	0.012	0.074	0.15	MVT-WS
6	-36 -16 7	0	0.53	0.60	1.8×10^{-5}	5.3×10^{-4}	0.0019	UVT-SC

Presenting response magnitudes



IntraClass Correlation (ICC)

- Reliability (consistency, reproducibility) of signal: extent to which the levels of a factor are related to each other
  - Example – 3 sources of variability: conditions, sites, subjects
  - Traditional approach: random-effects ANOVAs
  - LME approach

$$\hat{\beta}_{ijk} = \alpha_0 + \alpha_1 * x_k + b_i + c_j + d_k + \epsilon_{ijk},$$
$$b_i \sim N(0, \tau_1^2), c_j \sim N(0, \tau_2^2), d_k \sim N(0, \tau_3^2), \epsilon_{ijk} \sim N(0, \sigma^2)$$

$$ICC_l = \frac{\tau_l^2}{\tau_l^2 + \tau_2^2 + \tau_3^2 + \sigma^2}, l = 1, 2, 3$$

  - 3dICC_REML, 3dLME

Group Analysis: Non-Parametric Approach

- Parametric approach
  - Enough number of subjects $n > 10$
  - Random effects of subjects: usually Gaussian distribution
  - Individual and group analyses: separate

- Non-parametric approach
  - Moderate number of subjects: $4 < n < 10$
  - No assumption of data distribution (e.g., normality)
  - Statistics based on ranking or permutation
  - Individual and group analyses: separate

Group Analysis: Fixed-Effects Analysis

- When to consider?
  - LME approach
  - Group level: a few subjects: $n < 6$
  - Individual level: combining multiple runs/sessions
- Case study: difficult to generalize to whole population
- Model $\beta_i = b + \varepsilon_i$, $\varepsilon_i \sim N(0, \sigma_i^2)$, σ_i^2: within-subject variability
  - Fixed in the sense that cross-subject variability is not considered
- Direct fixed-effects analysis (**`3dDeconvolve/3dREMLfit`**)
  - Combine data from all subjects and then run regression
- Fixed-effects meta-analysis (**`3dcalc`**) : weighted least squares
  - $\beta = \sum w_i \beta_i / \sum w_i$, $w_i = t_i / \beta_i$ = weight for ith subject
  - $t = \beta \sqrt{\sum w_i}$

Non-Parametric Analysis

- Ranking-based: roughly equivalent to permutation tests
  - **3dWilcoxon** (~ paired *t*-test)
  - **3dFriedman** (~ one-way within-subject with **3dANOVA2**)
  - **3dMannWhitney** (~ two-sample *t*-test)
  - **3dKruskalWallis** (~ between-subjects with **3dANOVA**)
- Pros: Less sensitive to outliers (more robust)
- Cons
  - Multiple testing correction **limited** to FDR (**3dFDR**)
  - Less flexible than parametric tests
    - Can't handle complicated designs with more > 1 fixed-effects factor
    - Can't handle covariates
- Permutation approach?

Group Analysis Program List

* **3dttest++** (one-sample, two-sample and paired *t*) + covariates (voxel-wise)
* **3dMEMA** (R package for mixed-effects analysis, t-tests plus covariates)
* **3ddot** (correlation between two sets)
* **3dANOVA** (one-way between-subject)
* **3dANOVA2** (one-way within-subject, 2-way between-subjects)
* **3dANOVA3** (2-way within-subject and mixed, 3-way between-subjects)
* **3dMVM** (AN(C)OVA, and within-subject MAN(C)OVA)
* **3dLME** (R package for sophisticated cases)
* **3dttest** (mostly obsolete: one-sample, two-sample and paired *t*)
* **3dRegAna** (obsolete: regression/correlation, covariates)
* **GroupAna** (mostly obsolete: Matlab package for up to four-way ANOVA)

FMRI Group Analysis Comparison

<table>
<tr><th colspan="2"></th><th>AFNI</th><th>SPM</th><th>FSL</th></tr>
<tr><td colspan="2">t-test (one-, two-sample, paired)</td><td>3dttest++,
3dMEMA</td><td>Yes</td><td>FLAME1,
FLAME1+2</td></tr>
<tr><td colspan="2">One categorical variable:
one-way ANOVA</td><td>3dANOVA/2/3,
GroupAna</td><td>Only one WS factor:
full and flexible
factorial design</td><td>Only one within-
subject factor: GLM
in FEAT</td></tr>
<tr><td colspan="2">Multi-way AN(C)OVA</td><td>3dANOVA2/3,
GroupAna, 3dMVM</td><td>---</td><td>---</td></tr>
<tr><td colspan="2">Between-subject covariate</td><td>3dttest++,
3dMEMA, 3dMVM</td><td>Partially</td><td>Partially</td></tr>
<tr><td rowspan="4">Sophisticated
situations</td><td>Covariate +
within-subject
factor</td><td rowspan="4">3dLME</td><td rowspan="4">---</td><td rowspan="4">---</td></tr>
<tr><td>Subject
adjustment in
trend analysis</td></tr>
<tr><td>Basis functions</td></tr>
<tr><td>Missing data</td></tr>
</table>

Preview

- Basic concepts
  - Why do we need to do group analysis?
  - Factor, quantitative covariates, main effect, interaction, …
- Various group analysis approaches
  - Regression (*t*-test): 3dttest++, 3dMEMA, 3dttest, 3RegAna
  - AN(C)OVA: 3dANOVAx, 3dMVM, GroupAna
  - Quantitative covariates: 3dttest++, 3dMEMA, 3dMVM, 3dLME
  - Complicated cases: 3dLME
- Miscellaneous
  - Issues regarding result reporting
  - Intra-Class Correlation (ICC)
  - Nonparametric approach and fixed-effects analysis
- No routine statistical questions, only questionable routines!